Title (en)

AMINOESTER DERIVATIVES

Title (de)

AMINOESTERDERIVATE

Title (fr)

DÉRIVÉS AMINOESTÉRIFIÉS

Publication

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Application

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Abstract (en)

[origin: WO2015185649A1] The invention relates to novel compounds which are both phosphodiesterase 4 (PDE4) enzyme inhibitors and muscarinic M3 receptor antagonists, methods of preparing such compounds, compositions containing them and therapeutic use thereof. M3 Binging assay: CHO-KI clone cells expressing the human M3- receptor (Swissprot P20309) were harvested in Ca++/Mg++free phosphate-buffered saline and collected by centrifugation at 1500 rpm for 3 min. The pellets were resuspended in ice cold buffer A (15 mM Tris-HCl pH 7.4, 2 mM MgCl2, 0.3 mM EDTA, 1 mM EGTA) and homogenized by a PBI politron (setting 5 for 15 s). The crude membrane fraction was collected by two consecutive centrifugation steps at 40000 g for 20 min at 4°C, separated by a washing step in buffer A. The pellets obtained were finally resuspended in buffer B (75 mM Tris HCl pH 7.4, 12.5mM MgCl2, 0.3 mM EDTA, 1 mM EGTA, 250 mM sucrose), and aliquots were stored at - 80°C. The day of experiment, frozen membranes were resuspended in buffer C (50 mM Tris-HCl pH 7.4, 2.5 mM MgCb, 1 mM EDTA). The non selective muscarinic radio ligand [3H]-N-methyl scopolamine(Mol.Pharmacol.45:899-907) was used to label the M3 binding sites. Binding experiments were performed in duplicate (ten point concentrations curves) in 96 well plates at radioligand concentration of 0.1-0.3 nM. The non specific binding was determined in the presence of cold N-methyl scopolamine 10 uM. Samples (final volume 0.75 mL) were incubated at room temperature for 90 min. The reaction was terminated by rapid filtration through GF/B Unifilter plates and two washes (0.75 mL) with cold buffer C using a Packard Filtermate Harvester. Radioactivity on the filters was measured by a microplate scintillation counter TriCarb 2500 (PerkinElmer). Representative compounds of the invention, when tested in one of the above reported protocols, displayed an IC50 lower than 100 nM. Representative compounds of the invention displayed an IC50 lower than 100 nM in both PDE4 cell free and M3 binding assays.

IPC 8 full level

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